ROUTING AND ACTION

MEMORANDUM

ROUTING

TO:(1) Life Sciences Division (Strand, Micheline)

Report is available for review

(2) Proposal Files Report No.: Proposal Number: 56027-LS.8

DESCRIPTION OF MATERIAL

CONTRACT OR GRANT NUMBER: W911NF-09-1-0109

INSTITUTION: University of Medicine & Dentistry of New Jersey

PRINCIPAL INVESTIGATOR: Janine Santos

TYPE REPORT: Final Report

DATE RECEIVED: 10/20/16 9:59AM

PERIOD COVERED: 5/25/09 12:00AM through 8/24/13 12:00AM

TITLE: Final Report: Molecular mechanism of hTERT function in mitochondria

ACTION TAKEN BY DIVISION

(x) Report has been reviewed for technical sufficiency and IS [x] IS NOT [ ] satisfactory.

(x) Material has been given an OPSEC review and it has been determined to be non sensitive and, except for manuscripts and progress reports, suitable for public release.

(x) Perfomance of the research effort was accomplished in a satisfactory manner and all other technical requirements have been fulfilled.

(x) Based upon my knowledge of the research project, I agree with the patent information disclosed.

Approved by SSL\MICHELINE.STRAND on 11/4/16 1:11PM

ARO FORM 36-E

REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
20-10-2016	Final Report	25-May-2009 - 24-Aug-2013

4. TITLE AND SUBTITLE
Final Report: Molecular mechanism of hTERT function in mitochondria

5a. CONTRACT NUMBER
W911NF-09-1-0109

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
611102

6. AUTHORS
janine santos, nilesh sharma

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES
University of Medicine & Dentistry of New
185 South Orange Avenue

Newark, NJ 07101 -1709

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)
U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
56027-LS.8

12. DISTRIBUTION AVAILIBILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT
Human telomerase reverse transcriptase (hTERT) is localized to mitochondria, as well as the nucleus, but details about its biology and function in the organelle remain largely unknown. Using multiple approaches our studies revealed that mammalian TERT is mitochondrial, co-purifying with mitochondrial nucleoids and tRNAs. We demonstrate the canonical nuclear RNA [human telomerase RNA (hTR)] is not present in human mitochondria and not required for the mitochondrial effects of telomerase, which nevertheless rely on reverse transcriptase (RT) activity. Using RNA immunoprecipitations from whole cell and in organelle, we show that hTERT binds various

15. SUBJECT TERMS
mitochondria telomerase DNA metabolism

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Janine Santos
UU	UU	UU	UU		19b. TELEPHONE NUMBER 973-972-9729

Report Title

Final Report: Molecular mechanism of hTERT function in mitochondria

ABSTRACT

Human telomerase reverse transcriptase (hTERT) is localized to mitochondria, as well as the nucleus, but details about its biology and function in the organelle remain largely unknown. Using multiple approaches our studies revealed that mammalian TERT is mitochondrial, co-purifying with mitochondrial nucleoids and tRNAs. We demonstrate the canonical nuclear RNA [human telomerase RNA (hTR)] is not present in human mitochondria and not required for the mitochondrial effects of telomerase, which nevertheless rely on reverse transcriptase (RT) activity. Using RNA immunoprecipitations from whole cell and in organello, we show that hTERT binds various mitochondrial RNAs, suggesting that RT activity in the organelle is reconstituted with mitochondrial RNAs. In support of this conclusion, TERT drives first strand cDNA synthesis in vitro in the absence of hTR. Finally, we demonstrate that absence of hTERT specifically in mitochondria with maintenance of its nuclear function negatively impacts the organelle. Our data indicate that mitochondrial hTERT works as a hTR-independent reverse transcriptase, and highlight that nuclear and mitochondrial telomerases have different cellular functions.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
07/16/2012	7.00	N. K. Sharma, A. Reyes, P. Green, M. J. Caron, M. G. Bonini, D. M. Gordon, I. J. Holt, J. H. Santos. Human telomerase acts as a hTR-independent reverse transcriptase in mitochondria, Nucleic Acids Research, (09 2011): 0. doi: 10.1093/nar/gkr758
07/20/2012	6.00	Paula D. Green, Dong Kyun Woo, Janine H. Santos, Anthony D. D'Souza, Zenta Walther, W. David Martin, Brooke E. Christian, Navdeep S. Chandel, Gerald S. Shadel. Mitochondrial Genome Instability and ROS Enhance Intestinal Tumorigenesis in APCMin/+ Mice, The American Journal of Pathology, (01 2012): 0. doi: 10.1016/j.ajpath.2011.10.003
08/04/2011	4.00	Donna Gordon, Janine Santos. The emerging role of telomerase reverse transcriptase (TERT) in mitochondrial DNA metabolism, Journal of Nucleic Acids, (09 2010): 390791. doi:
TOTAL:	**3**	

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received		Paper
TOTAL:		

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received	Paper

TOTAL:

Number of Manuscripts:

Books

Received Book

TOTAL:

Received Book Chapter

TOTAL:

Patents Submitted

Patents Awarded

Awards

Graduate Students

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Nilesh Sharma	1.00
FTE Equivalent:	**1.00**
Total Number:	**1**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
Janine Santos	0.30	
FTE Equivalent:	**0.30**	
Total Number:	**1**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:	0.00
The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....	0.00
The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....	0.00
Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):.....	0.00
Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:.....	0.00
The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense	0.00
The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:	0.00

Names of Personnel receiving masters degrees

NAME
Total Number:

Names of personnel receiving PHDs

NAME
Total Number:

Names of other research staff

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

The studies funded by this award allowed better understanding of the role of TERT in mitochondria. Large strides were made in terms of its biochemical properties in the organelle as well as about the impact to normal cell biology upon overexpression or depletion of the mitochondrial content of the enzyme. Some of future studies speared by the work funded through this award are still hampered because of the lack of reagents to understand and isolate the mitochondrial versus nuclear function of the protein. Nevertheless, we now know that in the mitochondria only the catalytic component of telomerase is present, interacting with different types of nucleic acids, including DNA and RNA. The papers published during the time the award was funded attest for the advancement of the field and the productivity of the group.

Technology Transfer